REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

A. Claim Amendments.

Claims 3-5 and 17 are to be cancelled.

Claims 1, 2, 6, 9, 12 and 14-16 are currently being amended.

Claims 19-20 are being added.

After amendment, Claims 1-2, 6-16 and 18-20 will be pending in the application.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

The amendments to Claims 1, 2, 6, 9, 12 and 14-16, as well as the addition of Claims 19 and 20, are fully supported by the Specification as follows:

CLAIM #	CLAIM AMENDMENTS MADE	EXAMPLES OF SPECIFICATION SUPPORT
1	Growth factor is BDNF or NT-4/5; delivery into cortical tissues of the brain stimulates or supports neurons.	Paragraphs 0001, 0003; paragraphs 0007 and 0021 [BDNF supports numerous cell types]; paragraphs paragraphs 0006 and 0058-0063 [method stimulates growth and activity]; paragraphs 0014, 0019, and original Claims 3-5.

2	"Practice of the method" produces improvement of cognitive function.	Grammatical change to conform to antecedent limitations of Claim 1.
6	Growth factor is BDNF, NT-4/5 or NT-3—language is added for antecedent basis in Claim 1.	Paragraphs 0001, 0003, 0006, 0014, 0019, 0052-0064, and original Claims 3-5.
12	Stimulation of growth or activity.	Paragraphs 0052-0057 (Example III) and paragraphs 0058-0063 (Example IV) [BDNF levels and receptor expression increased].
9, 12, 14, 15	"EC" spelled out in Claims 9 and 12 as "entorhinal cortex," for clarification. References to path of neurons changed in Claims 14 and 15 to more technically accurate term "innervate."	Grammatical correction.
16	"Aging" wording rewritten to "aged" for grammatical clarity.	Grammatical correction.
New Claim 19	Response to practice of invention is in entorhinal cortical neurons.	Original Claim 12; paragraphs 0007, 0013, 0052-0057 (Example III) and 0058-0063 (Example IV) [BDNF levels and receptor expression increased].
New Claim 20	Response to practice of invention is in hippocampal neurons.	Original Claim 14; paragraphs 0007, 0013, 0052-0057 (Example III) and 0058-0063 (Example IV) [BDNF levels and receptor expression increased].

No new matter being added to the application, entry of the foregoing amendments is respectfully requested.

B. Response to New Matter Objection.

The Office Action objects to the claims as being directed to new matter to the extent that they extend to use of NGF in the claimed invention. Applicant respectfully submits that the objection is made moot by the foregoing amendments to the claims.

However, for the record, Applicant confirms his position that the use of NGF or nerve growth factors other than BDNF and NT-4/5 *is* encompassed by the present disclosure. Although the Examiner is correct that the focus of the disclosure is on the use of BDNF, NT-4/5 and other trkB receptor binding growth factors, it is not so limited.

The use of growth factors with "equivalent activity" which bind other receptors also present in trkB receptor containing tissues is contemplated by the disclosure (see, e.g., Paragraph 0003 [NGF and other nerve growth factors share structural and functional homologies with BNDF and NT-4/5). Although growth factors other than BDNF and NT-4/5 may not bind trkB receptors at physiologic concentrations, some do bind the receptor at the higher *in vivo* doses used in vector delivery. As such, NGF and other growth factors may bind trkB receptors if delivered according to the invention.

Moreover, the presence of trkB receptors in the claims defines the identity of the tissues to which neurotrophins are directed according to the invention, but the ability to bind those receptors is not mandatory.

B. Response to Rejection of Claims 1, 2 and 6-18 under Section 112, First Paragraph (Enablement)

The claims are rejected for lack of enablement with respect to the: **(a)** inclusion of NGF within the scope of the claims; **(b)** extent of guidance provided in the Specification regarding the structure of delivery constructs useful in the invention; **(c)** unpredictability of gene therapy outcomes generally; and as to **(d)** whether the benefit sought by practice of the invention is likely to be provided.

As discussed above, the first of these questions raised is moot in view of the amendments to the claims. As to issues **(b)** through **(d)**, Applicant submits that reconsideration of the application and art will reveal that the specification meets all of the criteria for enablement of the claims set forth in *In re Wands*, 8 USPQ2d 1400 (Fed.Cir.1988): (1) the quantity of experimentation necessary, (2) the amount of discretion or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Of the *Wands* factors, the Office Action focuses primarily on the second factor with respect to issue **(b)**, and the seventh factor with respect to issues **(c)** and **(d)** (Office Action at page 6). Applicant respectfully submits that the record in this and previously prosecuted applications based on similar disclosures (now issued U.S. patents) establish that practice of the invention as claimed is fully enabled.

1. Full Faith and Credit as to Previously Resolved Questions of Enablement.

MPEP 706.04 provides, in pertinent part:

> Full faith and credit should be given to the search and action of a previous examiner unless there is a clear error in the previous action or knowledge of other prior art. In general, an examiner should not take an entirely new approach or attempt to reorient the point of view of a previous examiner...

Applicant respectfully directs the Examiner's attention to examples of the inventor's previously issued U.S. patents to similar methods practiced in other regions of the brain; i.e., U.S. Patent Nos. 6,683,058 and 6,815,431. Based on essentially the same disclosure concerning the constructs to be used, the issue of enablement in these applications was resolved in favor of allowance of claims to the use of any suitable expression vector, to treat any neurodegenerative condition. As was confirmed during prosecution of these related prior patents, such vectors delivered to the brain are taken up by neurons for expression of a therapeutic neurotrophin

therein. Expression can persist for many months, without untoward responses to the vector or protein, such as inflammation.

The allowance of the claims referenced above in the parent application indicates that the question of whether the *in vivo* practice of the invention is enabled by the disclosure has already been decided in Applicant's favor. Therefore, **to the extent that the enablement rejection raises the same inquiries concerning the construction and fate of an expression vector and/or of an expressed neurotrophin in brain cells that were resolved in the '058 and '431 Patents**, that decision should be given "full faith and credit" with respect to the present claims as provided under MPEP 706.04.

2. Extent of Guidance in the Specification with Respect to the Choice and Construction of Expression Vectors for Use in the Invention.

Applicant respectfully submits that there is no compelling reason to believe that those of ordinary skill in the art could not readily choose, construct or utilize any expression vector adaptable to gene therapy in the non-dividing cells of the brain. Examples of such vectors are provided at paragraph 0027-0029 of the Specification, all of which are well-known to the art.

It is axiomatic that an inventor "does not need to include in the specification that which is already known to and available to one of ordinary skill in the art," to whom the specification is addressed. *Koito Manufacturing Co. Ltd., et al. v. Turn-Key-Tech, LLC.*, 381 F.3d 1142, 1155 (Fed.Cir. 2004), citing *Paperless Accounting, Inc. v. Bay Area Rapid Transit System*, 804 F.2d 659, 664 (Fed.Cir. 1986); *In re Lange*, 644 F.2d 856, 863 (CCPA 1981), and *In re Gay*, 309 F.2d 769, 774 (CCPA 1962). Thus, because the art has no need of guidance as to the selection and construction expression vectors for use in the brain beyond what the Specification provides, no more is required to satisfy the enablement requirements of Section 112, first paragraph.

3. Enablement as to the Practice of the Claimed Methods in the Cortices and Reasonable Expectations as to Outcomes.

One of ordinary skill in the art would, in light of the present teachings, reasonably expect to be able to practice the claimed invention and provide sufficient levels of BDNF or NT-4/5 growth factor (via expression or protein infusion) to stimulate and support neurons. The data provided in the Specification clearly confirm that such expectations would be well founded.

Delivery of growth factor (BDNF) into the brain was accomplished (Example I) in an animal model of relevance to aging and disease related degeneration in the brain (Paragraphs 0039-0040). Expression of BDNF was obtained (Example III), followed by upregulation of neurologically significant receptors in the entorhinal and hippocampal cortices (Example IV). The treated animals not only exhibited histological evidence of responsiveness to the claimed treatment, they also demonstrated improved cognitive function as compared to their pre-treatment condition (Example II).

Further experiments delivering BDNF using recombinant expression vectors have confirmed that the invention provides the stimulation of growth and activity, as well as promotion of survival, contemplated. As described in the first Declaration of Dr. Mark Tuszynski submitted herewith under 37 CFR §1.132, practice of the claimed invention in aged animals and animal models of neurodegenerative disease (Alzheimer's) established that it protected treated cortical neurons from cell death and atrophy resulting from injury (lesioning; see, Tuszynski Declaration at ¶ 3) or toxicity (from beta-amyloid, see, Declaration at ¶ 4).

Consistent with the examples provided in the Specification, treatment according to the invention also augmented the activity of treated neurons, as evidenced by improvements in cognition among treated animals. For example, in a transgenic animal model of Alzheimer's, spatial memory loss was reversed through treatment according to the invention (see, Tuszynski Declaration at ¶¶ 4-5 and 7). Further, the ability to perform specific hippocampal neuron-associated tasks was restored to animals treated according to the invention (see, Declaration at ¶¶ 4 and 6-7). All of these data establish that the practice of the invention, as disclosed and claimed, is enabled and effective to produce the desired benefits in treated subjects.

These results, while unique in the context of BDNF and NT-4/5 treatment of neurodegeneration *in the cortices*, are consistent with the results being obtained by the inventor from practice of the essential steps of the invention to deliver NGF to the primate and human forebrain and substantia nigra. The present invention is therefore part of a novel scheme for potentially successful gene therapy using a variety of growth factors.

The second enclosed Declaration of Dr. Mark Tuszynski (a copy of one originally submitted in the application for U.S. Patent No. 6,683,058) illustrates the point as to the successful delivery of NGF into the forebrain and substantia nigra using the same general approach now claimed for delivery of BDNF or NT-4/5 into the cortices. In non-human primate models of Alzheimer's (AD) and Parkinson's Disease (PD), NGF expression obtained was not only of sufficient volume (> 90% of neurons targeted were transfected) and duration (8+ months, at last testing) to offer a therapeutic benefit to treated animals, a demonstrable improvement in motor function and cognition was confirmed. See, e.g., data presented in the '058 Patent Tuszynski Declaration, at ¶ 3, 6, 12, 14-21 and 25-29. Although expression may decline over time, the expression which is achieved is sufficient to treat, and possibly even reverse, the cognitive and motor function impairment observed in the test animals. '058 Patent Tuszynski Declaration, at ¶ 3.

Notably, these results are achieved without detectable inflammation in the brain, thereby negating a common concern in gene therapy; i.e., the possibility of an immune attack on a viral vector. '058 Patent Tuszynski Declaration at ¶ 4, 6 and 12. The absence of an adverse immune response to administration of neurotrophin-expressing viral constructs in the brain is not altogether surprising. Immune responses to exogenous material in brain parenchyma (targeted in the invention) are usually muted, in contrast to responses observed in the ventricles or vascular circulation in the brain.

In the human clinical trials performed by the inventor, responses to expression of NGF introduced into the forebrain (using a technique similar to that now claimed for delivery of BDNF or NT-4/5 into the cortices) have been remarkable. For example, the rate of progression

of Alzheimer's Disease in the first patient treated with NGF is estimated to have been slowed by upwards of 51%, a heretofore unprecedented result in treatment of AD (see Tuszynski, *et al., Nat. Medicine,* 11:551-555, 2005, at 553, first column, enclosed). The *Nature Medicine* paper also reports promising results from a trial for treating Parkinson's Disease using a similar approach directed at the substantia nigra, at 553, second column.

Thus, on the basis of direct evidence supplied by the present disclosure, experience with the claimed technique using different neurotrophins, and previous determinations by the USPTO as to enablement of the practice of that technique, Applicant respectfully submits that it is clear that transfection and persistent expression in cortical brain cells to produce the biological effects to which the invention is directed can be achieved. Therefore, the enablement rejection has been fully addressed and overcome in this respect, and should be withdrawn.

C. Response to Rejection of Claims 1, 2, 6 and 11-17 under 35 U.S.C. Section 102(e).

This rejection is based on U.S. Patent No. 6,451,306, to the inventor and others. The '306 Patent relates to their work with *ex vivo* gene therapy; i.e., grafting growth factor expressing donor cells into the brain.

Although the present invention and the invention claimed in the '306 Patent relate to gene therapy for neurodegenerative conditions, the former is not anticipated by the latter. The '306 Patent teaches grafting of cells into the cholinergic forebrain, while the present invention focuses on gene and protein therapy of the cortices. However, for the purpose of streamlining prosecution, Applicant submits the suggested Declaration under 37 CFR 1.131 to remove the '306 Patent as prior art for anticipation or obviousness purposes. Reconsideration and withdrawal of the 102(e) rejection is therefore respectfully requested.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Atty. Dkt. No. 041673-2053

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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